

### **Remarks**

The present response is being submitted in reply to the Office action issued on November 21, 2005. Claims 1-65 are pending in this application, while claims 1-24, 43, 44, 46, 47 and 63-65 are withdrawn from consideration. By the present response, claims 25-44 and 48-62 have been amended and claim 45 has been canceled. No new matter has been added. Reconsideration is respectfully requested in light of the amendments being made hereby and of the following remarks.

### **Oath/Declaration**

The Examiner states that the declaration filed December 1, 2004 fails to comply with the provisions of 37 CFR 1.69 and MPEP §602.06 since the declaration is in a language other than English. The attorney for the Applicant had a telephone interview with the Examiner on December 7, 2005 whereby it was explained that an English declaration had been filed on May 24, 2005. The Examiner confirmed that the English declaration was received and was on file at the USPTO. Withdrawal of the requirement to file an English translation of the declaration is respectfully requested.

### **Objection to the Specification**

The specification has been objected to as failing to provide proper antecedent basis for the claimed subject matter of claim 37, i.e., “the process for the production of thermosensitive polymers according to claim 25, further comprising the step of pre-polymerizing the monomer solution for 5-120 seconds before dispersion in the organic phase.” Paragraph [000053] of the specification has been amended as set forth above to provide sufficient antecedent basis for the limitation of claim 37.

The disclosure is also objected to because of various other informalities, each of which is discussed below.

The phrase “IKA Werke” has been amended to “IKA Works, Inc.” in paragraphs [00088] and [00090].

The trademark terms TWEEN® and ULTRA-TURRAX® have been amended throughout the specification (i.e., paragraphs [00088], [00090] and [00091] to be capitalized, to include the symbol “®” and to include generic terminology. The applicant notes that the generic terminology for ULTRA-TURRAX® was already set forth in paragraph [00088], therefore a further amendment is not necessary (see “a thermal controlled dispersing vessel”). Regarding the term INSUMAN®, the applicant submits that the only instance of the term is in paragraph [00091] of the specification and it is already correctly set forth in capitalization, the symbol “®” and with generic terminology (see “an insulin solution”).

In light of the amendments to the specification, withdrawal of these objections to the specification is respectfully requested.

#### **Claim Objections**

Claims 25 and 26 are objected to for not having the word “a” prior to the phrase “mechanical comminution.” The Applicant respectfully submits that the article “a” is not needed prior to this phrase. The Applicant submits that the phrase “mechanical comminution” is not used as a noun in claims 25 and 26, which would require use of the preceding article “a,” but rather as a verb or process, akin to the use of the terms “agitation” or “homogenization.” Withdrawal of this objection is respectfully requested.

The phrases “nano- or microparticles” and “nano or microparticles” have been amended to “nano- or micro- particles” (or “nano- or micro- particle”, as the case may be) in claims 25, 26, 32 and 53. Withdrawal of this objection is also respectfully requested.

The applicant notes that, regarding claims 32 and 53, the term “polyer” has been amended to correctly read “polymer.”

**Rejection of claims 25-42, 45 & 48-62 under 35 U.S.C. 112, second paragraph**

Claims 25-42, 45 & 48-62 have been rejected under 35 U.S.C. 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. The Examiner states the following rejections.

In paragraph 15 of the Office action, the Examiner states that claims 25 and 26 recite the limitation “the production” in line 1, for which there is insufficient antecedent basis, and the Examiner suggests changing the wording to “a production.”

Claims 25 and 26 (and claim 53) have been amended to define the thermosensitive polymers, rather than refer to claim 1, since claim 1 currently stands as withdrawn. However, the applicant respectfully disagrees with the Examiner’s suggestion that “the production” should be amended to “a production.” As set forth in M.P.E.P. 2173.05(e), a claim is indefinite when it contains words or phrases whose meaning is unclear. Obviously, however, the failure to provide explicit antecedent basis for terms does not always render a claim indefinite. If the scope of the claim would be reasonably ascertainable by those skilled in the art, then the claim is not indefinite. *Ex parte Porter*, 25 USPQ2d 1144, 1145 (Bd. Pat. App. & Inter. 1992). Furthermore, the

Examiner's focus during examination of claims for compliance with the requirement for definiteness of 35 U.S.C. 112, second paragraph, is whether the claim meets the threshold requirements of clarity and precision, not (emphasis added) whether more suitable language or modes of expression are available (M.P.E.P. 2173.02). M.P.E.P. 2173.02 encourages Examiners to suggest claim language to applicants to improve clarity or precision of the language used, but should not reject claims (emphasis added) or insist on their own preferences if other modes of expression selected by applicants satisfy the statutory requirement. In reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the Examiner must consider the claim as a whole to determine whether the claim appraises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph, by providing clear warning to others as to what constitutes infringement of the patent (M.P.E.P. 2173.02). The applicant respectfully submits that the scope of these claims is clearly reasonably ascertainable by those skilled in the art. The inclusion of the term "the" prior to "production" does not render these claims indefinite, nor does it affect the scope of the claims in any way whatsoever. Requiring such an amendment is beyond the focus during examination of claims for compliance with the requirement for definitiveness and is therefore unnecessary. Withdrawal of this rejection is strongly requested.

In paragraph 16 of the Office action, the Examiner states that claims 25, 26 and 53 recite the limitation "the steps" in line 2, for which there is insufficient antecedent basis, and the Examiner suggests changing the wording to "steps."

In paragraph 19 of the Office action, the Examiner states that claims 28 and 30

include the vague and indefinite phrase “the steps” in line 3, and the Examiner suggests amending the term to “steps.”

In paragraph 22 of the Office action, the Examiner states that claim 30 includes the vague and indefinite phrase “the steps” and suggests changing the phrase to “step.”

In paragraph 24 of the Office action, the Examiner states that claim 25 includes the phrase “the steps,” and suggests changing the phrase to “steps.”

In paragraph 25 of the Office action, the Examiner states that claims 35, 37, 38, 39 and 41 include the vague and indefinite phrase “the step,” and suggests changing the term to “a step.”

In paragraph 27 of the Office action, the Examiner states that claims 49, 51, 56, 58, 59 and 61 include the vague and indefinite phrase “the step,” and suggests changing the phrase to “a step.”

The Applicant respectfully repeats the argument set forth above regarding the requirement to change “the production” to “a production.” Additionally, the Applicant respectfully submits that it is common practice to positively recite the steps of a “process” claim and whether the general reference to the steps of the process is done by “the steps” or “steps” does not affect the scope of the claims, would not render the claims indefinite and one skilled in the art would reasonably be able to ascertain the scope of the claims. Withdrawal of this rejection is respectfully requested.

In paragraph 17 of the Office action, the Examiner states that claims 27, 51, 54 and 60 recite the limitation “the group” in line 2, for which there is insufficient antecedent basis, and the Examiner suggests changing the wording to “a group.”

In paragraph 21 of the Office action, the Examiner states that claims 29, 33, 35, 40, 42, 48 and 57 recite the limitation “the group” in line 3, and the Examiner suggests changing the term to “a group.”

In paragraph 23 of the Office action, the Examiner states that claims 30 and 38 recite the limitation “the group” in line 4, for which there is insufficient antecedent basis, and suggests changing the term to “a group.”

In paragraph 28 of the Office action, the Examiner states that claims 50, 28, 61 and 62 recite the limitation “the group,” for which there is insufficient antecedent basis, and suggests changing the limitation to “a group.”

The applicant respectfully disagrees with the Examiner on each of these rejections. Each of these claims comprises a Markush group set forth in the format “...selected from the group consisting of A, B and C.” Referring to M.P.E.P. 2173.05(h), alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. One acceptable form of alternative expression, which is commonly referred to as a Markush group, recites members as being “selected from the group consisting of A, B and C” (emphasis added). See *Ex parte Markush*, 1925 C.D. 126 (Comm’r Pat. 1925). Clearly, the Markush group format presented in each of these claims complies with the format established as acceptable by M.P.E.P. 2173.05(h). Withdrawal of this rejection is strongly requested.

In paragraph 18 of the Office action, the Examiner states that claims 27-45 and 48-62 include the vague and indefinite term “thermosensitive polymers” and the

Examiner suggests adding the term “the” prior to “thermosensitive polymers.”

The applicant notes that each of claims 27-45 and 48-62 have been amended accordingly. Withdrawal of this rejection is requested.

In paragraph 20 of the Office action, the Examiner states that claims 28 and 49 include the vague and indefinite phrase “0.05 to 30% mol co-monomers” for which it is unclear whether the phrase means concentration of co-monomers added or co-monomer content.

The Applicant submits that claims 28 and 49 have been amended accordingly to clarify this matter. In addition, support for the amendments may be found in the specification at paragraphs [000055] and [000057]. Withdrawal of this rejection is therefore requested.

In paragraph 26 of the Office action, the Examiner states that claim 45 provides for the use of the thermosensitive polymers, but since the claim does not set forth any steps involved in the method/process, it is unclear what method/process is intended to be encompassed.

The Applicant submits that claim 45 has been canceled. Therefore, any objection or rejection to this claim is no longer germane and should be withdrawn.

Based on the arguments and discussion set forth above, withdrawal of each rejection under 35 U.S.C. 112, second paragraph, is respectfully requested.

**Rejection of Claims 25, 26, 28-31, 35-38, 45, 49-52 and 56-58 under 35 U.S.C. 102(b)**

Claims 25, 26, 28-31, 35-38, 45, 49-52 and 56-58 have been rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 6,204,033 (Müller-Schulte). The

Examiner argues that Müller-Schulte anticipates these claims by teaching a process for a production of thermosensitive polymers comprising the steps of dispersing at least one of magnetic or metallic colloids in an aqueous monomer solution, suspending the aqueous monomer solution through mechanical comminution in an organic phase that is not miscible with water after addition of a multifunctional cross-linking agent and a radical initiator and radically polymerizing the organic phase to nano- or micro-particles (Abstract). The Examiner essentially further argues that Müller-Schulte teaches every limitation set forth in the aforementioned claims.

The Applicant now respectfully refers to MPEP §706.02(b), which provides that a rejection based on 35 U.S.C. 102(b) can be overcome by:

- (a) Persuasively arguing that the claims are patentably distinguishable from the prior art;
- (b) Amending the claims to patentably distinguish over the prior art; or
- (c) Perfecting priority under 35 U.S.C. 119(e) or 120 by amending the specification of the application to contain a specific reference to a prior application or by filing an application data sheet which contains a specific reference to a prior application in accordance with 37 CFR 1.78(a).

The Applicant respectfully submits that the present invention is patentably distinct from the invention disclosed in this reference. Specifically, each and every feature of the present invention as recited in claims 25, 26, 28-31, 35-38, 45, 49-52 and 56-58 are not taught or disclosed in Müller-Schulte, and therefore the reference does not anticipate the



present invention. Moreover, it would not be obvious to one skilled in the art to have amended the invention as set forth in Müller-Schulte to incorporate the features of the present invention as set forth in the presently rejected claims.

The Applicant respectfully submits that the Müller-Schulte reference relates to a process for producing polyvinyl alcohol (PVAL) particles containing a magnetic colloid encapsulated inside. The reference does not teach or disclose whether these polyvinyl alcohol particles are thermosensitive or whether they have a physical structure changeable by magnetic induction, as required by instant claims 25 and 26. The Applicant also disagrees that the Abstract of Müller-Schulte even mentions “thermosensitive polymers.” After a careful review of the Müller-Schulte reference, including the Abstract and the entire disclosure, the Applicant submits that Müller-Schulte fails to teach or disclose any reference of thermosensitive polymers.

According to Müller-Schulte, the polyvinyl alcohol particles are prepared by dispersing a magnetic colloid in an aqueous polymer (PVAL) solution, and by adding this mixture to an organic phase (such as an oil phase). While the mixture is stirred to suspend the aqueous polymer solution in the oil phase, a bi-functional cross-linking agent is added to cross-link the polymer chains of the PVAL. This results in PVAL particles having a magnetic colloid encapsulated inside. This process is described in the Abstract, in claim 1, and in the following passages of the specification of Müller-Schulte: col. 5, line 58 – col. 6, line 49; Example 1. Basically, the particles disclosed in Müller-Schulte are obtained by the cross-linking of a pre-existing polymer, polyvinyl alcohol.

The Examiner further argues, in paragraph 30 of the Office action, that the Abstract of Müller-Schulte discloses a radical initiator and that the reference discloses radically polymerizing the organic phase to nano- or micro-particles. However, this description of Müller-Schulte relates to the optional grafting process which may be performed after having prepared PVAL particles, as described above. This grafting process is described in Müller-Schulte at col. 7, lines 19-55, in claim 14 and in Example 24.

Furthermore, the monomers (vinyl monomers) discussed in the Abstract of Müller-Schulte are not polymerized to particles, as the particles were already produced in a preceding step. To the contrary, these monomers are grafted onto the surface of the PVAL particles, as explained in col. 7, lines 19-55 of Müller-Schulte. The monomers of present claims 25 and 26 are polymerized to produce the polymeric backbone of the particles (i.e., “polymerizing said organic phase to nano- or micro-particles”). The polymeric backbone of the PVAL particles of Müller-Schulte is not generated by radical polymerization of monomers, as in the present invention, but rather by chemical cross-linking of pre-existing polymer chains (PVAL).

Still further, according to the process steps defined in present claims 25 and 26, the cross-linking agent and the radical initiator are present simultaneously within the polymerization reaction mixture. To the contrary, when performing the graft polymerization step recited at the end of the Abstract of Müller-Schulte, the cross-linking agent that was initially used for cross-linking the PVAL is no longer present, and no

additional cross-linking agents are added. In the radical polymerization reaction (also referred to as “grafting” in Müller-Schulte), the reaction mixture contains only PVAL particles (acting as the grafting substrate), vinyl monomers and cerium salt as a polymerization initiator (see Example 24, and col. 7, lines 19-35 of Müller-Schulte). No cross-linking agent is added to this reaction mixture. Although a cross-linking agent is initially used for cross-linking the polyvinyl alcohol chains to generate the polymer particles (Example 1; glutaraldehyde as a cross-linker), this cross-linker is no longer present at the time when the grafting reaction is performed. The remaining free cross-linker molecules that were not incorporated into the cross-linked PVAL polymer particles are removed during the washing steps performed prior to the grafting reaction (see Example 24 of Müller-Schulte). Moreover, for the purpose of the grafting reaction, the presence of cross-linking agents would not even make any sense and would even be detrimental to the reaction. In summary, Müller-Schulte fails to teach the presence of a multifunctional cross-linking agent during the radical polymerization. The Applicant notes that the reaction described in Example 1 (paragraph [000088]) of the present specification, N,N'-methylene bisacrylamide is used as the multifunctional cross-linking agent, acrylamide is used as the monomer and APS/TEMED is used as the radical initiator.

With respect to claims 30, 31, 51 and 52, Müller-Schulte also fails to teach adding magnetic particles of 10-200 nm to a radical polymerization reaction. The graft polymerization reaction referred to at the end of the Müller-Schulte Abstract (and claim 14 and col. 7) utilizes PVAL particles produced by the cross-linking process described in

Müller-Schulte. These particles have a size of 1-10 µm – well above 10-200 nm.

With respect to claims 35, 36, 56 and 57, Müller-Schulte fails to teach adding a surfactant to the radical polymerization reaction (please note claim 14 & col. 7, lines 19-33, in particular). The passages noted by the Examiner at the top of page 10 of the Office action refer to emulsion cross-linking of PVAL, and not to a radical polymerization reaction.

With respect to claim 37, the Applicant respectfully disagrees that Müller-Schulte teaches a step of pre-polymerizing a monomer solution. The passage noted by the Examiner (col. 9, lines 23-33) merely teaches how the magnetic colloid is dispersed in an aqueous solution of polyvinyl alcohol and polyvinyl pyrrolidone, which is then suspended in vegetable oil in the presence of surfactants.

Therefore, because each and every feature of the present invention as recited in claims 25, 26, 28-31, 35-38, 45, 49-52 and 56-58 are not taught or disclosed in Müller-Schulte, the Applicant submits that the reference does not anticipate the present invention. It is respectfully requested that this rejection be withdrawn.

**Rejection of Claims 34 and 55 under 35 U.S.C. 102(b)**

Claims 34 and 55 have been rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 6,204,033 (Müller-Schulte) in light of U.S. Patent No. 5,990,262 (Shishikura, et al.). It is initially noted that the rejection should have been raised under 35 U.S.C. 103(a) since two references are being used, i.e., it should have been an obviousness rejection. The Examiner argues that Müller-Schulte teaches a process for a

production of thermosensitive polymers, as discussed in the previous rejection, and further teaches that organic solvents such as hexane, heptane, cyclohexane, or petroleum ether are used in the process for the production of the thermosensitive polymers (col. 7, lines 45-51). However, the Examiner notes that Müller-Schulte fails to specifically disclose that these organic phase solvents have a polar solubility parameter of 5-10 (cal/cm<sup>3</sup>)<sup>1/2</sup>. The Examiner refers to Shishikura, et al. and argues that the reference teaches that heptane has a solubility parameter of 7.4 (cal/cm<sup>3</sup>)<sup>1/2</sup> and concludes that one skilled in the art would recognize that the organic solvent of Müller-Schulte would inherently have solubility parameter as disclosed by Shishikura, et al.

The Applicant respectfully disagrees with this rejection for at least the above-discussed deficiencies of Müller-Schulte. Moreover, Shishikura, et al. clearly fails to make up for any of said deficiencies of Müller-Schulte. Müller-Schulte relates to a grafting process using pre-existing polymer particles as a substrate, as set forth in col. 7, lines 19-51 of the reference. This process is performed in the presence of cerium salts and in the absence of cross-linking agents. Clearly, the solvents set forth in col. 7 of Müller-Schulte are used for a different purpose than in the present invention.

Therefore, because each and every feature of the present invention as recited in claims 34 and 55 are not taught or disclosed in Müller-Schulte, even when taken in consideration of Shishikura, et al., each and every limitation of the present invention is not taught or disclosed and so the reference (or combination of references) does not anticipate the present invention. It is respectfully requested that this rejection be

withdrawn.

**Rejection of claims 27, 32, 33, 48, 53 and 54 under 35 U.S.C. 103(a)**

Claims 27, 32, 33, 48, 53 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Müller-Schulte in view of U.S. Patent No. 6,133,047 (Elaissari, et al.).

According to the Examiner, Müller-Schulte teaches a process for a production of thermosensitive polymers as discussed above, but fails to teach a process for a production of thermosensitive polymers, wherein the aqueous monomer solution comprises at least one monomer selected from a group consisting of N-isopropylacrylamide (NIPAM), N-substituted acrylamides and N-substituted methacrylamides. The Examiner relies on Elaissari, et al. for this missing teaching of Müller-Schulte and concludes that it would have been obvious for one skilled in the art to include the process of Müller-Schulte with a use of encapsulated magnetic colloids having a polymer core consisting of polystyrene and a well known heat-sensitive polymer such as NIPAM, as taught by Elaissari, et al., in order to generate thermosensitive polymeric particles, which may be used to isolate at least one biological molecule from a liquid specimen.

The applicant respectfully submits that to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference (or references when combined) must teach or suggest all of the claim limitation. Applicant respectfully submits that one skilled in the art would have no suggestion or motivation to combine the aforementioned references in order to arrive at the present invention. Additionally, even

if one skilled in the art were to consider Müller-Schulte alone, or in combination with Elaissari, et al., each and every limitation of the present invention would not be disclosed, nor would there be a reasonable expectation of success if the aforementioned references were to be considered. Still further, a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention (M.P.E.P. 2141.02 VI; *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)).

The Applicant again disagrees with the Examiner's rejection for at least the numerous deficiencies of Müller-Schulte, which have been discussed at length above. The teachings of Elaissari, et al. fail to make up for any of the many deficiencies of Müller-Schulte. Furthermore, and referring first to present claims 27 and 48, the Examiner suggests in the Office action at the first paragraph of page 13 that it would have been obvious to include encapsulated magnetic colloids having a polymer core of polystyrene and using a heat-sensitive polymer such as NIPAM (N-isopropylacrylamide) as taught by Elaissari, et al. in the process of Müller-Schulte. As explained above, Müller-Schulte teaches to encapsulate magnetic colloids in polyvinyl alcohol particles by cross-linking polymeric PVAL in a water-in-oil emulsion and in the presence of surfactants. Radical polymerization is only used according to Müller-Schulte for modifying the magnetic PVAL particles by "grafting."

The Applicant respectfully questions the ability of one skilled in the art to have included NIPAM into the PVAL particles of Müller-Schulte. These particles are produced by cross-linking of PVAL which requires PVAL to be present as an aqueous

solution to be suspended in an organic phase (see Abstract of Müller-Schulte). NIPAM is a monomer and, as such, could not be used to directly replace PVAL. Also, it is unknown whether poly-NIPAM can be dissolved in water and be cross-linked in the same way as PVAL.

Furthermore, Müller-Schulte emphasizes the fact that PVAL particles contain reactive hydroxyl groups on their surface (see Abstract) which could be used for grafting reactions or for coupling biomolecules to the surface (col. 7, lines 19-33; claim 11). In this regard, Müller-Schulte teaches away from the presently claimed invention. Therefore, one skilled in the art would have clearly refrained from replacing PVAL with different polymers not having reactive hydroxyl groups.

When producing magnetic particles according to Elaissari, et al., a core consisting of a first polymer is covered with a “magnetic layer” which is based on a second polymer (e.g., poly-NIPAM) and which has magnetic material embedded therein. This magnetic layer is obtained by polymerization of suitable monomers. The particles of Elaissari, et al. comprise a core based on a first polymer, an internal layer covering this core and containing magnetic material, and an external or encapsulation layer (col. 2, lines 23-41). In contrast, the process of Müller-Schulte does not require using a first polymer (see col. 5, lines 21-41) and does not require a step of obtaining a core based on a first polymer. The magnetic particles are instead directly embedded into the PVAL particles during the cross-linking process.

Therefore, due to the fundamental differences between the processes of Elaissari, et al. and Müller-Schulte, it would not have been obvious for one skilled in the art to



replace PVAL with poly-NIPAM in the process of Müller-Schulte. The process described in Elaissari, et al. comprises at least three separate polymerization steps (steps a, b – e) in claim 9, whereas the process of Müller-Schulte is essentially a one-step cross-linking reaction which is performed in an water-in-oil emulsion.

In addition, present claims 25 and 26 require the aqueous monomer solution to be suspended through mechanical comminution in an organic phase that is not miscible with water, after adding a multifunctional cross-linking agent. This step is not taught by Müller-Schulte and is clearly not set forth in Elaissari, et al. Although Müller-Schulte teaches a step of suspending an aqueous solution in an organic phase (Abstract), this step pertains to a cross-linking reaction in which polyvinyl alcohol is cross-linked in a suspension (col. 5, lines 19-20), rather than to a radical polymerization reaction. When compared to the process taught by Elaissari, et al., the process of the present invention requires only one polymerization step vs. (at least) three separate polymerization steps in Elaissari, et al. (see col. 2, lines 27-41), and is therefore easier to perform, less time-consuming and less expensive. Since the process of Müller-Schulte relies on cross-linking of existing polymers (PVAL) rather than on radical polymerization, it clearly would not have been obvious to one skilled in the art to have included a polymer such as poly-NIPAM and polystyrene-based magnetic particles into the PVAL particles of Müller-Schulte.

The Applicant further submits that Elaissari, et al. also fails to teach particles that are thermosensitive, as recited in the present claims (see also paragraphs [00031] – [000033]). It appears that the iron content (or the proportion of magnetic material) in

these particles is too low and therefore, inductive heating by applying an external, high-frequency magnetic alternating field is not possible. Consequently, in the passages describing the potential uses of the particles, Elaissari, et al. does not teach or disclose any possible applications that would rely on inductive heating.

Referring to claims 32, 33, 48 and 54 (i.e., the possibility of using magnetic colloids encapsulated in a core polymer), the Applicant submits that Müller-Schulte clearly advises against using polystyrene-encapsulated magnetic colloids (col. 3, lines 5-9, 22-26) and, according to the teaching of Müller-Schulte, it is considered advantageous that the magnetic colloids can be dispersed directly into the polymer phase without being encapsulated beforehand (col. 5, lines 21-28). Also, when using encapsulated magnetic colloids as a starting material, the dispersibility in the aqueous phase may be reduced (col. 5, lines 15-22). Furthermore, the use of encapsulating polymers carrying hydroxyl groups (as some of the polymers listed in claim 33) may interfere with glutaraldehyde cross-linking of the PVAL. For at least these reasons, Müller-Schulte also teaches away from the present invention and so the Applicant submits that one skilled in the art would not have had any motivation to use encapsulated magnetic colloids in connection with the process set forth in Müller-Schulte.

In light of the aforementioned deficiencies of the combination of teachings of Müller-Schulte and Elaissari, et al., the Applicant respectfully submits that the combination of references fails to teach every limitation set forth in the presently rejected claims and that due to these deficiencies, one skilled in the art would not have been motivated to combine these references to arrive at the present invention, and also that said

teachings in fact teach away from the presently claimed invention. Withdrawal of this rejection is strongly requested.

**Rejection of claims 39-41 and 59-61 under 35 U.S.C. 103(a)**

Claims 39-41 and 59-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Müller-Schulte in view of U.S. Patent No. 4,375,399 (Havas, et al.). According to the Examiner, Müller-Schulte teaches a process for a production of thermosensitive polymers as discussed above, but fails to teach a process for a production of thermosensitive polymers, further comprising a step of encapsulating active agents in the polymers by adding the active agents to a monomer solution containing at least one of magnetic or metallic colloids. The Examiner relies on Havas, et al. for this missing teaching of Müller-Schulte and states that the methods of encapsulating proteins and enzymes in polymers are well known in the art. The Examiner concludes that it would have been obvious for one skilled in the art to include the method of Müller-Schulte with a method of mixing polymers, such as polyvinyl alcohols, with active agents, such as proteins or enzymes, as taught by Havas, et al. in order to incorporate active agents in thermosensitive polymers at the time of polymerization.

The Applicant disagrees with the Examiner's rejection for at least the numerous deficiencies of Müller-Schulte, which have been discussed at length above. Moreover, Havas, et al. fails to make up for the deficiencies of Müller-Schulte. As noted above, Müller-Schulte fails to teach a process by which thermosensitive polymers can be obtained by suspending an aqueous monomer solution, which also contains magnetic or metallic colloids, in an organic phase that is not miscible with water, after adding a

multifunctional cross-linking agent and a radical initiator, and by polymerizing this reaction mixture.

The Applicant submits that even if one skilled in the art would have modified the method of Müller-Schulte by including active agents such as proteins or enzymes, as taught by Havas, et al. into the PVAL solution, this would not have resulted in the process of instant claims 39-41 and 59-61, since the particles of Müller-Schulte are produced by a suspension cross-linking process (col. 5, lines 16-20), rather than by a radical polymerization process as required by the present claims.

It must also be taken into account that the cross-linking reaction taught by Müller-Schulte is performed in a water-in-oil emulsion with an excess of oil (col. 6, lines 35-38). Apparently, the process taught by Havas, et al. does not use a water-in-oil suspension. Therefore, as the presence of active agents such as proteins or enzymes may potentially interfere with the formation and stability of this water-in-oil suspension, the Applicant submits that one skilled in the art would not even have been motivated to add these agents to the PVAL solution. Moreover, these agents may interfere with the glutaraldehyde cross-linking of the PVAL or with the emulsifiers added to the oil phase, thus yielding particles having shapes or sizes which are not acceptable (see, for instance, Müller-Schulte col. 3, lines 55-60).

Furthermore, Müller-Schulte emphasizes the advantage of being able to use the magnetic PVAL particles for various purposes, due to the basic chemical functionality of the basic polymer, PVAL (col. 7, lines 4-18). In particular, subsequent modification of the PVAL particles by “grafting” is considered advantageous (col. 7, lines 19 ff.; col. 7,

line 56 – col. 8, line 7). The basic teaching of Müller-Schulte is that magnetic PVAL particles should first be prepared by the specified suspension cross-linking process, and should then be modified as required by the particular field of application. In view of this teaching, and considering the potential disadvantages, the Applicant submits that one skilled in the art would not have even considered modifying the teaching of Müller-Schulte as suggested by the Examiner.

In light of the aforementioned deficiencies of the combination of teachings of Müller-Schulte and Havas, et al., the applicant respectfully submits that the combination of references fails to teach every limitation set forth in the presently rejected claims and that due to these deficiencies, one skilled in the art would not have been motivated to combine these references to arrive at the present invention. Withdrawal of this rejection is strongly requested.

**Rejection of claims 42 and 62 under 35 U.S.C. 103(a)**

Claims 42 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Müller-Schulte in view Havas, et al., and further in view of U.S. Patent No. 5,529,777 (Andrianov, et al.). According to the Examiner, Andrianov, et al. teaches a method of encapsulating an antigen, wherein the antigen is mixed with a polymer solution, microparticles are rapidly formed of the polymer and antigen to form a stable biodegradable microparticle (col. 5, lines 23-28), which can be used as an immunogenic vaccine composition (col. 15, lines 3-10). The Examiner also states that Andrianov, et al. teaches that polymers comprising carbohydrates, which includes glucose, are used in the method of encapsulating an antigen (col. 9, lines 1-11). The Examiner concludes that it

would have been obvious for one skilled in the art to include in the method of Müller-Schulte in view of Havas, et al. with a method of using biodegradable polymers such as glucose as taught by Andrianov, et al. in order to encapsulate an active agent in polymers for use in therapeutic settings, where biodegradable polymers are desirable.

The Applicant disagrees with the Examiner's rejection for at least the numerous deficiencies of Müller-Schulte and Havas, et al., which have been discussed at length above. The Applicant submits that claims 42 and 62 are dependent on claims 39-41 and 59-61, respectively, which require the active agent to be added to the monomer solution which is then polymerized. Andrianov, et al. relates to an entirely different type of process according to which the antigen is mixed with a polymer solution whereby particles are rapidly formed of the polymer and antigen without the use of organic solvents. (See Andrianov, et al., col. 5, lines 22-26 and col. 13, lines 46-54). This is contrary to present claims 25 and 26 ("...aqueous monomer solution ... in an organic phrase that is not miscible with water"). The Applicant respectfully submits that even if one skilled in the art would have modified the method of Müller-Schulte by including polyvalent alcohols or carbohydrates, the combination would not have resulted in the method as presently claimed which requires that these substances be added to the monomer mixture (See Example 1 of the present specification).

In light of the aforementioned deficiencies of the combination of teachings of Müller-Schulte, Havas, et al. and Andrianov, et al., the applicant respectfully submits that the combination of references fails to teach every limitation set forth in the presently rejected claims and that due to these deficiencies, one skilled in the art would not have

been motivated to combine these references to arrive at the present invention.

Withdrawal of this rejection is strongly requested.

### **Double Patenting**

The Examiner has rejected claims 25, 26, 28, 30-33, 35, 49, 51-54 and 56 as being unpatentable over claims 1-9 and 14 of Müller-Schulte. The Examiner argues that although the conflicting claims are not identical, they are not patentably distinct from each other.

The Applicant disagrees with the Examiner's double patenting rejection for at least the numerous deficiencies of Müller-Schulte, which have been discussed at length above. In particular, the Applicant respectfully disagrees with the Examiner's conclusion that "each teaches a process for a production of thermosensitive polymers comprising steps of dispersing magnetic or metallic colloids in an aqueous monomer solution ... and radically polymerizing the organic phase." Müller-Schulte does not teach a process for the production of thermosensitive polymers, and the process of Müller-Schulte does not comprise dispersing magnetic or metallic colloids in an aqueous monomer solution. Moreover, the particles of Müller-Schulte are not generated by radical polymerization of monomers, but rather by cross-linking of PVAL polymers.

Clearly, the process of Müller-Schulte is fundamentally different from that of the presently claimed invention, and therefore the Applicant submits that the claims of Müller-Schulte cannot be interpreted as encompassing the claims of the present application. The claims of Müller-Schulte do not pertain to a process for producing thermosensitive polymers by radical polymerization of monomers. Therefore, the


Applicant strongly requests that the double-patenting rejection be withdrawn.

**Conclusion**

In light of the foregoing claims and arguments, it is believed that the present application is in condition for allowance, and such action is earnestly solicited. The Examiner is invited to call the undersigned if there are any remaining issues to be discussed which could expedite the prosecution of the present application.

Respectfully submitted,

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By:   
D. Peter Hochberg  
Reg. No. 24,603

D. Peter Hochberg Co., L.P.A.  
1940 E. 6<sup>th</sup> St. – 6<sup>th</sup> Floor  
Cleveland, OH 44114  
(216) 771-3800  
DPH/sm